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INSTITUTE FOR DEFENSE ANALYSES

# Report of the Workshop on Chemical Agent Toxicity for Acute Effects

## Institute for Defense Analyses
## May 11-12, 1998

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# PREFACE

This document was prepared by the Institute for Defense Analyses in partial fulfillment of the Task Order "Support for Quadrennial Defense Review (QDR) — Analysis of Defense Against Chemical/Biological Weapons," sponsored by the Assistant to the Secretary of Defense for Nuclear, Chemical and Biological Defense Programs.

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## A. INTRODUCTION

The potential use of chemical agents against US forces is becoming a prominent concern. This is true not only in major theaters of war, but also in lesser contingencies and operations other than war where the US military could face insurgents or terrorists with access to these deadly materials. For US forces to have the best defenses against chemical agents, those responsible for developing these defenses must have the best available estimates of agent toxicity and associated risks.

There is an inherent tension between the stringency of protective measures and the operational burden of implementing them. Because of this, defenses against chemical agents typically strive to ensure sufficient protection while minimizing disruption to military operations. If toxicity—here used to mean the median lethal or effective dosage or dose, and the degree of variation in human response—is underestimated, defenses may not provide sufficient protection. Unacceptable chemical casualties could occur. If toxicity is overestimated, protective measures could be overly burdensome (and, perhaps, overly expensive). Force effectiveness could be diminished and unacceptable additional conventional casualties could occur.

Estimating chemical agent toxicity is, however, a challenging scientific effort that draws on animal studies and their extrapolation to humans, limited direct data on human reaction to these agents, and even more limited data regarding the results of chemical agent use on the battlefield. Various studies have produced different toxicity estimates over the years, and there have been generally accepted estimates that have been documented in Army field manuals and other official sources. In 1994, the US Army Chemical Defense Equipment Process Action Team published the results of an extensive reexamination of the sources of toxicity estimates for the agents GA, GB, GD, GF, VX, and HD. This report is generally referred to as the Reutter-Wade report [1]; it recommended human toxicity estimates appropriate for defending the soldier. Many of the recommended estimates were markedly different from those that had been accepted for decades.

This report was carefully reviewed. One review, by the Army Science Board [2], recommended that the Reutter-Wade estimates be adopted on an interim basis while further data were collected. Another, by the Committee on Toxicity of the National Research Council [3], proposed accepting some estimates on an interim basis, while

suggesting that others be raised or lowered based on their [the Committee's] opinion of the quality of existing data. Moreover, some individuals in the chemical defense community felt, based on their own experience and on previous reviews, that some of the Reutter-Wade estimates were not as valid as other estimates.

Because of the importance of these estimates to those responsible for developing chemical defense equipment, estimating medical requirements, and analyzing the effects of chemical weapons against US forces, Mr. Walter Hollis, Deputy Under Secretary of the Army for Operations Research, asked the Joint NBC Board Secretariat to convene a workshop to (1) reach a consensus on interim toxicity parameters for the six agents mentioned above, (2) specify guidelines for their use, and (3) identify high priority areas for future work to improve these estimates. This workshop was held May 11 and 12, 1998, at the Institute for Defense Analyses, and included representation from the chemical defense community, the medical community, the analytical community, three Services, the Joint Service Integration Group, and the Joint Service Material Group (workshop participants are listed in the Appendix). This paper summarizes the results of this workshop.

## B. WORKSHOP RESULTS

### 1. Scope

In order to keep the problem tractable, the sponsor requested that the workshop focus on:

- Acute effects, as opposed to chronic effects or effects from low-level exposures;
- 70 kilogram male soldiers, as opposed to civilians or female military personnel;
- Military scenarios, as opposed to use against civilians; and
- Neat versions of the six agents, as opposed to other agents or modified versions of the six agents.

All other variations are recognized as important, but there are substantial data shortfalls with regard to these situations; they will be identified below as areas where further work needs to be done.

## 2. Toxicity Estimates

The workshop participants discussed each toxicity estimate at length, and consensus was reached on each one. Tables 1 through 6 summarize the consensus values, along with some of the caveats that arose during the discussion. Each estimate comprises two values, a median and a probit slope. Notes that summarize key issues raised during the discussions follow the tables. Numbers identifying the notes are given in braces in the tables.

Units for doses are milligrams. Percutaneous liquid values are for the total applied dose to a 70-kg man (the applied dose is assumed to be completely absorbed). All percutaneous vapor and small particle aerosol values pertain to 30-minute exposures for individuals without clothing. For nerve agents, percutaneous vapor exposure estimates are for masked soldiers with eye protection.

Units for dosages are milligram-minutes/meter$^3$. All inhalation values pertain to two-minute exposures and are for a minute volume (MV) of 15 liters.

**Table 1. GA Toxicity Values**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| GA | LCt50 | Percutaneous vapor | 15000/5 {1} |
| GA | LCt50 | Inhalation vapor | 70/12 |
| GA | ECt50, threshold {2} | Percutaneous vapor | 2000/5 {3} |
| GA | ECt50, severe {4} | Percutaneous vapor | 12000/5 {3} |
| GA | ECt50, severe {4} | Inhalation vapor | 50/10 |
| GA | ECt50, mild {5} | Inhalation vapor | 1/5 {6}{14} |
| GA | LD50 | Percutaneous liquid | 1500/5 {1} |
| GA | ED50, severe {4} | Percutaneous liquid | 900/5 {1} |

**Table 2. GB Toxicity Values [1]**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| GB | LCt50 | Percutaneous vapor | 12000/5{7} |
| GB | LCt50 | Inhalation vapor | 35/12 |
| GB | ECt50, threshold {2} | Percutaneous vapor | 1200/5 {3} |
| GB | ECt50, severe {4} | Percutaneous vapor | 8000/5 {3}{8} |
| GB | ECt50, severe {4} | Inhalation vapor | 25/10 |
| GB | ECt50, mild {5} | Inhalation vapor | 1/5 {9}{14} |
| GB | LD50 | Percutaneous liquid | 1700/5 {1} |
| GB | ED50, severe {4} | Percutaneous liquid | 1000/5 {1} |

[1] An objection was raised following the conclusion of the workshop regarding the derivation of the GB inhalation LCT50. Because this value is used as the basis for other G-agent values, its accuracy is critical. IDA's examination of this objection is summarized in a memorandum for the record (Appendix A). Although the objection was valid, there is sufficient evidence to warrant retaining the Reutter-Wade value and, hence, the workshop recommendation.

**Table 3. GD Toxicity Values**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| GD | LCt50 | Percutaneous vapor | 3000/6 {10} |
| GD | LCt50 | Inhalation vapor | 35/12 |
| GD | ECt50, threshold {2} | Percutaneous vapor | 300/6 {3} |
| GD | ECt50, severe {4} | Percutaneous vapor | 2000/6 {3}{11} |
| GD | ECt50, severe {4} | Inhalation vapor | 25/10 |
| GD | ECt50, mild {5} | Inhalation vapor | 0.4/6 {3}{14} |
| GD | LD50 | Percutaneous liquid | 350/6 {1} |
| GD | ED50, severe {4} | Percutaneous liquid | 200/6 {1} |

**Table 4. GF Toxicity Values**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| GF | LCt50 | Percutaneous vapor | 3000/5 {10} |
| GF | LCt50 | Inhalation vapor | 35/12 |
| GF | ECt50, threshold {2} | Percutaneous vapor | 300/5 |
| GF | ECt50, severe {4} | Percutaneous vapor | 2000/5 |
| GF | ECt50, severe {4} | Inhalation vapor | 25/10 |
| GF | ECt50, mild {5} | Inhalation vapor | 0.4/5 {14} |
| GF | LD50 | Percutaneous liquid | 350/5 {1} |
| GF | ED50, severe {4} | Percutaneous liquid | 200/5 {1} |

**Table 5. VX Toxicity Values**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| VX | LCt50 | Percutaneous vapor | 150/6 {12} |
| VX | LCt50 | Inhalation vapor | 15/6 {1} |
| VX | ECt50, threshold {2} | Percutaneous vapor | 10/6 {3} |
| VX | ECt50, severe {4} | Percutaneous vapor | 25/6 |
| VX | ECt50, severe {4} | Inhalation vapor | 10/6 |
| VX | ECt50, mild {5} | Inhalation vapor | 0.1/4 {3}{14} |
| VX | LD50 | Percutaneous liquid | 5/6 {1} |
| VX | ED50, severe {4} | Percutaneous liquid | 2/6 {1} |

**Table 6. HD Toxicity Values**

| Agent | Parameter | Route of Entry | Value/Probit Slope |
|---|---|---|---|
| HD | LCt50 | Percutaneous vapor | 10000/7 {15} |
| HD | LCt50 | Inhalation vapor | 1000/6 {1}{16} |
| HD | ECt50, threshold, moderate temperature {13} | Percutaneous vapor | 50/3 {17} |
| HD | ECt50, threshold, hot temperature {13} | Percutaneous vapor | 25/3 {17} |
| HD | ECt50, severe, moderate temperature {18} | Percutaneous vapor | 500/3 {17} |
| HD | ECt50, severe, hot temperature {18} | Percutaneous vapor | 200/3 {17} |
| HD | ECt50, severe {19} | Ocular vapor | 100/3 {3} |
| HD | ECt50, mild {19} | Ocular vapor | 25/3 {3} |
| HD | LD50 | Percutaneous liquid | 1400/7 {1} |
| HD | ED50, severe {18} | Percutaneous liquid | 600/3 {1}{20} |

## Notes for Tables 1-6

{1} The workshop participants agreed that data did not support much precision with regard to probit slope. Hence, the Reutter-Wade value was rounded to a whole number.

{2} As used here, threshold refers to a slight ChE inhibition.

{3} There are no data to justify a probit slope, but the recommended value can be used as an interim value until such time that data are available.

{4} For organophosphate nerve agents, severe effects are systemic, similar to lethal effects.

{5} Inhalation vapor ECt's include ocular exposure. The term "mild" refers to a level of symptom (ocular, rhinorrhea, and/or chest tightness) that might be noticed in the field.

{6} There were very few data to support an estimate of this value (or of the corresponding value for GB, from which values for GA were frequently derived). Given the lack of data and the recommendation of the NRC to raise the value provided by Reutter-Wade, the workshop accepted 1.0 as an interim value, with a probit slope of 5. These values should not be used under conditions where this effects curve crosses a more severe effects curve.

{7} There was considerable discussion regarding whether the value in Reutter-Wade was consistent with poorly-documented anecdotal field experience, which appears to argue for a larger value. Although the better-documented scientific studies, including human studies, point toward a value of 10000, it was agreed that a somewhat larger value could be justified. It was also agreed that, for battlefield purposes, inhalation was a more critical entry route than percutaneous for Army and Air Force personnel. A Navy representative, however, noted that penetration of ship spaces with chemical agents where personnel were masked but not suited could lead to a condition where percutaneous exposure was dominant.

{8} Reutter-Wade did not provide an estimate for this toxicity value, although several other sources appeared to be consistent.

{9} The workshop recommended a value of 1.0 with the caveat that more research was needed. Moreover, the probit slope of 5 is not based on data, but can be used as an interim value. This includes ocular exposure.

{10} The LCt50 value was increased slightly from the Reutter-Wade value, both to indicate lack of precision in the estimate (there are no human data) and to be consistent with the increase in the LCt50 for GB.

{11} Few data are available; this ECt value was based on the assumption that GD is four times as toxic as GB.

{12} The LCt50 value applies to unclothed individuals and null wind conditions. Different clothing conditions and wind speeds would produce different numbers.

{13} Threshold effects are defined as the midpoint of a dosage range at which effects begin to occur in the sample population.

{14} This curve should only be used when not superceded by a more severe condition.

{15} Observed mortality rates from HD in World War I, together with reports written in the 1940s and data from non-human primate studies, suggest the value for HD percutaneous vapor proposed by Reutter-Wade may be too low. The Reutter-Wade value is based on a review of animal studies that calculated mortality based on vesication, to which humans are the most vulnerable species. That study discounted data from non-human primate studies, since non-human primates are highly resistive to vesication. However, the mechanism of mortality from HD percutaneous vapor is currently unknown. Some data suggest that mortality may not result from vesication but from immune suppression and other effects similar to those caused by radiation. Non-human primates provide a very good model for radiation injuries in humans; if HD is in fact radiomimetic, greater weight should be given to data from non-human primate studies suggesting a higher value. This would be more consistent with experience in battlefield use of HD, as well. For these reasons, the workshop agreed that a higher median value was warranted.

{16} Animal studies tend to support the value of 900 provided by Reutter-Wade, whereas historical evidence appears to support a higher value. The workshop agreed that 1000 was a defendable number.

{17} This condition assumed masked soldiers with eye protection.

{18} For HD, severe effects consist of vesication.

{19} This effect category was renamed ocular vapor since the effects are specific to the eye and are not systemic. Moderate temperatures are assumed.

{20} The Reutter-Wade median was rounded to 600 to avoid false precision, as suggested by the NRC. The probit slope was increased to 3 to be consistent with other non-lethal effects.

## 3. Guidelines for Use

As with all human toxicity estimates, the recommended estimates are valid only for the given exposure conditions. All human toxicity estimates have inherent confidence limits around them. These confidence limits are a function of the dose-response curve and the underlying data upon which the estimates are based. Because of the extrapolation necessary (from animals to humans and/or from less-than-optimal toxicological data) in formulating the estimates, the confidence limits cannot be well defined. Users will encounter situations that include conditions that vary from the given exposure conditions for the estimates in this report. Often, this will require further review of references and/or coordination with others to develop solutions to these problems. In these cases, the estimates in this report will serve as a solid basis for departure and further extrapolation. In all cases, it is important to thoroughly document references and methodologies that are used.

There are key differences between the nature of the effects of nerve and mustard agents. The medical effects of nerve agent exposure by any route are attributable to inhibition of the enzyme acetylcholinesterase (either locally or systemically); the signs and symptoms observed will depend on factors such as route of exposure and dosage.

In contrast, the medical effects of sulfur mustard (HD) exposure differ by the route of exposure because significantly different mechanisms of injury are involved:

- Lethality by inhalation of HD vapor at high concentrations occurs by an unknown mechanism.
- Lethality by percutaneous exposure to liquid mustard (and presumably high concentrations of percutaneous vapor) is due to immunosuppression of the bone marrow and peripheral white blood cells/lymphocytes. Death is usually attributed to overwhelming systemic infection.
- Non-lethal exposures to percutaneous vapor result in "classic" vesication (blistering) of the exposed skin surface due to specific effects at the dermal-epidermal junction (the impact of secondary bacterial infections is not considered).
- Ocular vapor exposures result in direct irritation to the eye (which doesn't actually blister).

As noted previously, values for vapor inhalation apply to two-minute dosages. It is common practice to invoke Haber's law and assume that these values apply for exposures of different durations. But this is not true for G-agents. The panel observed

that the value for 10-minute exposure is 1.67 times that of a 2-minute exposure. The inhalation values for the G-agents can probably be extrapolated from 2 minutes through 60 minutes with reasonable confidence. The accuracy of extrapolating below 2 minutes and beyond 60 minutes is unknown. Methods of performing these extrapolations were not addressed or agreed upon at this meeting. As a general rule, the greater the extrapolation from the original data, the greater the resulting uncertainty.

Mustard agents appear to become more toxic as exposure time increases, because there are no detoxification or homeostatic compensatory mechanisms. The exact relationship between Ct and exposure time is not known.

Also as noted, percutaneous vapor values are for 30-minute exposures. The accuracy of extrapolations beyond two hours is unknown.

Probit slopes allow casualties to be calculated at lower and higher values than the medians, using standard methods. Extrapolations below the $16^{th}$ percentile and above the $84^{th}$ have low reliability.

Percutaneous vapor values are for unclothed individuals. There are no agreed-upon conversion factors for clothed individuals.

As noted earlier, all the inhalation values in the tables are appropriate for minute volumes of 15 liters per minute. Some participants at the workshop observed that inhaled dosages are roughly linearly proportional to the minute volume, up to volumes of 50 liters. Hence, if the minute volume is doubled to 30 liters, the inhaled amount is also doubled and the LCt50 is halved. However, it was also noted that at least one source[2] reported that for GB, an increase in minute volume by a factor of 4 resulted in a Ct value that was 36 percent of the original value.

These values all apply to 70 kg male soldiers. These agents will be of different toxicity to female soldiers, because of weight differences and gender differences, and will be more toxic to the general population. Factors of 2 and 10 for the general population or sensitive subgroups were mentioned at the workshop, but there was no consensus on these values.

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[1] Franke, Major Siegfried, *Textbook of Military Chemistry*, Military Publisher of the German Democratic Republic, Berlin, 1977.

## C. RECOMMENDATIONS FOR FUTURE EFFORTS

It is clear from the notes to the tables and from the above discussion that, in spite of decades of research, there is still considerable uncertainty about the effects of chemical agents, particularly when extrapolated from central estimates. It is also clear that the primary data supporting much of the earlier work are no longer available. Thus, a major recommendation of the workshop is to prepare a permanent archive of data relevant to the estimation of chemical agent toxicity. Much information was collected in the process of preparing the Reutter-Wade report that could provide the core of such an archive. It may be impossible to repeat many of these experiments, so ensuring the long-term availability of this information will be a valuable service. Reproducing this archive in DTIC would ensure widespread availability to future researchers.

Additional efforts are required to address situations not covered by these estimates. These include:

- Longer exposures and lower concentrations,
- The effect of clothing,
- Mixed populations (male and female soldiers, civilians).

In some cases, laboratory research is needed, while in others, such as with civilians, laboratory research is infeasible and community agreement on appropriate adjustment factors is needed.

There is also a requirement to address the methodology used by analysts to employ these values in risk assessments. Probit-based methodologies may not be suitable for all cases, particularly when effects are different for different routes of entry or when effects may result from more than one route of entry, such as for HD. Toxic load and other candidate methodologies should be explored to determine if they provide better estimates of agent effects. However, studies to generate additional data may be needed to test alternative methodologies.

Some members of the workshop felt that there was a need for an analysts' handbook, fully describing the ranges in which the existing estimates are valid, and providing rules of thumb for adjustments when those ranges are exceeded. Example standard calculations and full references to the aforementioned data archives would also be provided.

The workshop did not reach a consensus on which additional agents or on which different forms of agents (such as dusty agents) needed to be addressed next with regard to establishing agreed toxicity values. This prioritization needs to originate in the policy community rather than in the research community.

Finally, there was concern expressed regarding the validity of past work, if it was based on values different from those agreed upon at this workshop. Each situation must be viewed separately. In some cases, parameter changes may make little difference in the results. There were presentations made at the workshop that suggested that changes in probit slope values may not produce large differences in the results of some analyses. In other cases, it may be that only relative, rather than absolute, results are important, and changes in toxicity values may not change the relative rankings of outcomes. In yet other cases, programmatic decisions may have already been made that would be difficult or expensive to revisit. For new work especially, however, these values should be used unless there are significant and well-documented reasons for deviating. These values are the best estimates we have for these six agents, and they represent the consensus of representatives of the scientific, medical, analytical, and operational communities based on extensive examination of available data and careful review of that examination.

# REFERENCES


[1] Reutter, Sharon A. and Wade, John V., LTC., Edgewood Research, Development and Engineering Center, "Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier, (U)" ERDEC-SP-018, March 1994. (SECRET)

[2] Army Science Board, "Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier," April 1995.

[3] National Research Council Subcommittee on Toxicity Values for Selected Nerve and Vesicant Agents, *Review of Acute Human-Toxicity Estimates for Selected Chemical-Warfare Agents*, National Academy Press, Washington, D.C., 1997.


**OTHER REFERENCES OF INTEREST**


[4] Life Systems, Inc., "Information for Combat Developers on Performance Effects from Exposure to Mustard Agent," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-6C, December 16, 1997.

[5] Life Systems, Inc., "Information for Combat Developers on Performance Degrading Effects from Exposure to G-Nerve Agents," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-10B, December 16, 1997.

[6] Life Systems, Inc., "Information for Combat Developers on Performance Degrading Effects from Exposure to VX," submitted to U.S. Army Center for Health Promotion and Preventive Medicine, TR-1605-11B, December 16, 1997.

[7] Memorandum, Walter W. Hollis to General William W. Crouch, "Guidelines for Application of Toxicity Estimates," November 3, 1997.

[8] Memorandum, Stephen L. Kistner to Director, Ballistics Missile Defense Organization, "Toxicity Values for Use in the Post-Engagement Ground Effects Model," November 12, 1997.

[9] Memorandum, Col. Patricia L. Nilo to the Joint Service Integration Group and the Joint Service Material Group, "Membership on Integration Product Team—Application of Chemical Agent Toxicity Estimates," December 23, 1997.

[10] Memorandum, Stephen L. Kistner to Commander, U.S. Army Edgewood Research, Development and Engineering Center, "Clarification of Rationale for Toxicity Values," March 9, 1998.

[11] Memorandum, Col. Robert E. Hilliard to Deputy Commander, U.S. Army Space and Missile Defense Command, Missile and Space Technology Center, "Summary of Toxicity Values for the Post Engagement Ground Effects Model," March 19, 1998.

## APPENDIX A: MEMORANDUM FOR THE RECORD

**S**trategy, **F**orces and
**R**esources **D**ivision

*Jeffrey H. Grotte, Deputy Director*

# Memorandum

| | | | |
|---|---|---|---|
| TO | The Record | DATE \| | 25 May 2001 |
| FROM | J. H. Grotte | | |
| SUBJECT | Regarding GB Toxicity Estimates Presented in the Toxicity IPT Workshop | | |

**Background**

The report of the Toxicity IPT Workshop held at the Institute for Defense Analyses during May, 1998, has not been released. Although all participants left the workshop agreeing that the values for agent toxicity that had been developed during the workshop were a suitable set of *interim* values for the modeling of chemical agent effects from a defensive standpoint, subsequent objections were raised. The objection of continuing concern is the proposed value for the GB two-minute inhalation $LCT_{50}$. The Workshop adopted the value published in the Reutter-Wade (RW) report[3]. This value is 35 mg-min/$m^3$, half of the previously-accepted value of 70 mg-min/$m^3$ published in FM 3-9. Toxicity values for other G agents are based on this value, hence concerns for this value translate into concerns for other values.

The RW value for inhalation $LCT_{50}$ for a two-minute exposure to GB was derived from a table of values on page 231 of the RW report, which gives ten-minute $LCT_{50}$s for several animal species. RW estimates the human $LCT_{50}$ by fitting a power function (linear in terms of logarithms of both dependent and independent variables) relating ten-minute $LCT_{50}$ to the independent variable MV/WT (minute volume divided by mass). The value for man is determined by evaluating the fit function at MV/WT equal to 0.214, and multiplying the result by 0.6 to obtain the two-minute $LCT_{50}$[4].

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[3] Reutter, Sharon A. and Wade, John V., LTC, Edgewood Research, Development and Engineering Center, *Review of Existing Toxicity Data and Human Estimates for Selected Chemical Agents and Recommended Human Toxicity Estimates Appropriate for Defending the Soldier*, ERDEC-PS-018, March 1994. (SECRET)

[4] Multiplying by 0.6 is a statement that Haber's Law, which says that effective dosage is independent of exposure time, does not hold for GB.

Based on archival human data, the Committee on Toxicology of the National Research Council (NRC) recommended that the RW value be further lowered to some unspecified value, to be determined by future research. Pending such research, the Workshop accepted the RW estimated human GB $LCT_{50}$ as an acceptable interim value.

Two objections have been raised to this value. The first concern was that reproducing the regression resulted in a different value (two-minute $LCT_{50}$ = 45). Further discussions with Dr. Reutter revealed this discrepancy to be due to the fact that the RW methodology rounded the MV/WT values to one decimal place before performing the fit, but did not note this step in the report.

The second objection was that the mass and minute volume for the pig provided in the source data table were significantly different from the pig used in the $LCT_{50}$ determination. To be sure, the RW report cautions that "values given for weight and respiratory parameters do not necessarily apply to the experimental population for which the $LCT_{50}$ was determined" for any of the species, but the appropriate pig values were: mass equal to 7.5 kg and minute volume equal to 3.53 l/min, according to the source material [Silver[5]].

**Discussion**

One can argue whether rounding before performing the regression was methodologically optimal. The rationale for doing so was that three-decimal place precision was unwarranted given natural species variation and the caveat noted above that the independent variables were not specific to the experimental populations used. The difference between the two-minute human values (45 for the unrounded case, 37 for the rounded case) is small given the uncertainties in the population characteristics and the $LCT_{50}$ determinations.

The pig values are somewhat more difficult to resolve. The table below gives two-minute human $LCT_{50}$ values for a variety of "corrections" based on regressions performed at IDA.

| ***Correction*** | ***Resulting 2-minute human $LCT_{50}$*** |
|---|---|
| Omitting pig data | 55 mg-min/m3 |
| Omitting pig data and rounding | 46 mg-min/m3 |
| Substituting small pig | 50 mg-min/$m^3$ |
| Substituting small pig and rounding | 46 mg-min/$m^3$ |

[5] Silver, S. D, *The Estimation of the Toxicity of GB to Man*, MLRR 23, Chemical Corps Medical Laboratories Research Report, Army Chemical Center, MD, June 1953, declassified report.

Given these results, it is possible to speculate that if the appropriate pig data had been used, or if the pig data had not been included, or if the regressions were performed prior to rounding, RW might have produced a different estimate for human two-minute $LCT_{50}$. However, given that: 1) the differences between the RW value of 35 mg-min/$m^3$ and the values in the above table are relatively small (considering the uncertainties inherent in estimating toxicity), 2) the RW value is more conservative from a defensive perspective than any of the revised values, 3) the NRC has cited human data indicating a potentially lower value[6], and 4) recent analyses[7] performed at the Edgewood Chemical Biological Center on the data cited in Silver produce a two-minute $LCT_{50}$ value of 29 mg-min/$m^3$, the RW value appears to be a reasonable estimate.

Hence, we feel that there is little to be gained at this point by altering this estimate, which is likely to change as more research is conducted, and considerable value in releasing the Toxicity IPT Workshop Report.

It is important to remember that a number of recommendations made by the Workshop *differ* from the RW values. Small changes were made in values for the percutaneous vapor $LCT_{50}$ for G-agents, in the $ED_{50}$ (severe effects) value for VX percutaneous liquid, and in the $LCT_{50}$ value for HD inhalation vapor. Probit slope values were rounded to the nearest integer values for all agents. A significant change was made for the HD percutaneous vapor $LCT_{50}$ value, where the Workshop recommended using the higher value contained in FM 3-9 rather than the RW value. Further, the Workshop recommended values for the percutaneous vapor $ECT_{50}$ (severe effects) for G-agents, and provided estimates for probit slopes not presented in RW.

The purpose of the Workshop was to provide the defense community a consistent set of values that could be used by analysts addressing chemical agent issues. In the absence of the Workshop report, analysts are constrained to use the official FM 3-9 values (which do not include probit slopes at all), although there is growing consensus that these are not sufficiently conservative, or the unofficial RW values, which some analysts are already using in their studies. The Workshop values provide a more complete set of estimates that have been reviewed and adjusted by the Workshop participants, who represented "the chemical defense community, the medical community, the analytical community, three services, the Joint Service Integration Group, and the

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[6] These data are presented for GB in Table 16 on page 92 of the Reutter-Wade report. In addition, on page 232 and elsewhere, RW refers to an unpublished report by James. Although the language on page 232 appears to indicate that the James report justifies only the RW regression methodology, a private communication from Dr. Reutter indicates that this report also supports the 35 value as well. IDA has not had an opportunity to review this unpublished report.

[7] A briefing and accompanying material were presented to visitors to the Edgewood Chemical Biological Center from IDA and OSD(S&TR) on May 21, 2001. The methodology used fit $LCT_{50}$ values for a variety of animals from the Silver reference to a function using body mass and exposure times as independent variables.

Joint Service Materiel Group.[8]" Releasing this report with the interim GB $LCT_{50}$ value would fulfill the original intent of the Workshop sponsor to provide a baseline of toxicity values that the defense community could share in a consistent manner to address critical chemical defense issues.

[8] From the Report of the Workshop.

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Although many studies and experiments have been performed over many years to establish the toxicity of chemical weapons agents, estimates of lethal and effective dosages vary considerably. A recent study by the US Army reviewed all available past data and recommended a set of lethality values. This study was reviewed by the National Research Council, which proposed changes to some of the recommendations of the Army study. Because a consistent, agreed-upon set of toxicity values is vital to the development of chemical defensive measures, the US Army Office of the Deputy Chief of Staff for Operations sponsored a workshop at the Institute for Defense Analyses that brought together key representatives of the chemical defense community to reach a consensus on interim toxicity values for the agents GA, GB, GD, GF, VX, and HD. The results of this workshop are summarized in this document.

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